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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SAUCIER, SANDRA E	
ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,988	MEIR, URL	
	Examiner	Art Unit	
	Sandra Saucier	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *78,98-115 and 119-123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *78,98-115,119-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 78, 98-115, 119-123 are pending and are under examination.

Claim Rejections - 35 USC § 112

Claims 78, 98-115, 119-123 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the freezing of semen from different species with a cryoprotectant, does not reasonably provide enablement for the freezing any biological matter, particularly with no cryoprotectant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The invention is in the field of cryopreservation of biological matter for future medical/veterinary use.

The working examples are all directed to the freezing/thawing of suspension of sperm in extenders which contain cryoprotectants such as glycerol, glucose, egg yolk etc..

The claims encompass the freezing of any biological matter including tissues, organs, and any type of cells with and without cryopreservatives.

The state of the art is as follows.

Freezing technology with regard to biological materials is an art with centuries of experimentation. The state of the art with regard to organs and tissues and "simple" multicellular structures is still far from satisfactory. Please see the review by Gosden [U] which teach that ovarian tissue banking which includes freezing of the tissue is still an experimenta procedure (abstract). This means that it is not routine to freeze all types of tissue. See also the review by I.A.M. de Graaf *et al.* [V] where it is taught that tissue preservation by freezing is still not routine and that cryopreservation by vitrification appears to be the most promising route of cryopreservation for tissue and organs with retention

of viability/function of the tissue or organ. Further, organs, because of their size, are particularly susceptible to freezing injury.

A second consideration is the fact that even with single cell suspensions, not all cells react the same with regard to freezing protocol, in fact even with a single mammalian cell, the oocyte, there are significant species differences. See Dinnyes *et al.* [W], a review that states on page 722, "Although sperm cells have been frozen successfully in dogs and cats, cryopreservation of oocytes in dogs remains elusive.".

Luvoni [X] on page 510 section 3.4, states that sperm cells and embryos of cats have been successfully frozen, but "freezing of [cat] oocytes is still considered experimental because adequate rates of survival, fertilization and embryo development of frozen oocytes have been reached mainly with murine oocytes.". Thus, even freezing of single cells with retention of function is dependant on cell type and even the species from which it is derived.

While the instant claims do not require any cryopreservative, the art of freezing cells or tissues without cryopreservatives is non-existent except in the food art. However, freezing food is distinct from the instant application where the frozen material is to be employed in medical procedures such as IVF, transplantation and other medically related purposes. The criteria for a successful freezing/thawing protocol of a frozen dinner is much lower than for a gamete, for example.

Also, the type of cryopreservative for a particular cell type is also critical and is an area of unpredicability. The type and concentration of cryopreservative is derived empirically, see Guillouzo *et al.* [U2] where for one cell type, hepatocytes, critical parameters are the choice of the cryoprotectant and the composition of the freezing medium (abstract). On page 9, it is disclosed that even the species from which the hepatocytes are derived requires changes in the freezing medium composition for best results.

In short, freezing of cells, tissues and organs is still an art with great unpredictability in terms of successful freezing of even the various types of single cells in suspension, coupled with the unpredicability of the concentrations and types of cryoprotectants for each cell type.

Undue experimentation would be required to practice the invention as claimed due to the amount of experimentation necessary because of the limited amount of guidance and limited number of working examples in the specification, the nature of the invention, the state of the prior art, breadth of the claims and the unpredictability of the art.

Claim Rejections - 35 USC § 103

Claims 78, 98-115, 119-123 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,873,254 [IDS].

The claims are directed to a method for changing the temperature of a sample comprising:
(i) changing the temperature of the sample by subjecting it to a temperature gradient from an initial to an intermediate temperature,
(ii) subjecting the sample to the intermediate temperature until the sample uniformly reaches the intermediate temperature,
(iii) changing the temperature of the sample until it reaches a final temperature, wherein the sample exceeds 0.5 cm in at least two mutually perpendicular cross sections and wherein the initial, intermediate and final temperatures are different and all progress in either a higher or lower sequence from one another.

US 5,873,254 teaches a method of changing the temperature of a sample comprising: subjecting the sample to a temperature gradient to change the temperature of the sample from an initial temperature to an intermediate temperature, held at the constant intermediate temperature, then changing to a final temperature (col. 5, ls. 40-60, col. 6). The temperature is a constant -7C as the sample moves through block 14. This corresponds to maintaining the

temperature by pausing the sample. Whether the temperature is maintained at an intermediate level by pausing the sled or having the block uniformly the same intermediate temperature as the sled moves through appears to be an element of experimental design because the result is the same, i.e. maintenance of the same temperature in the sample for a period of time. This reference teaches a freezing method based on directional freezing as the material is moved through a temperature gradient so that the cooling rate and ice propagation front are precisely controlled, instead of the more familiar and common multi-directional heat transfer methods.

The reference lacks the explicit stipulation of the size of the sample as exceeding 0.5cm in each of two mutually perpendicular cross-sections.

In the generic description of the invention (Summary of Invention), no limitation as to the size of the sample is described. Thus, the generic description is non-limiting with regard to size of sample.

While the size of the sample in the exemplification is ABOUT 1cm X 1cm x 0.5mm (col. 6, l. 15), use of the term "about" permits a variation of undefined range around this measurement. Please see MPEP 2144 IV A where it is stated that changes in size, shape or sequence of adding ingredients is *prima facie* obvious. Mere scaling up of a prior art process is not sufficient to patentably distinguish over the art in the absence of other evidence.

Claims 78, 98-115, 119-123 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,873,254 [IDS] in combination with US 4,131,200 [A] in light of Dayian *et al.* [V2].

The claims and US 5,873,254 have been discussed above. Also, please note that no dimensions have been stipulated which might limit the size of the apparatus and no negative limitations have been used to limit the size of the samples used in the controlled freezing method of US '254.

US 4,131,200 discloses a bag designed for freezing biological materials such as platelets. The dimensions of the bag are 9.3 cm by 10.2 cm. The method of Dayian *et al.* was used to test the bags. Dayian *et al.* teach a PC concentration of about 57 mls, see footnote on Table 1A. A calculation of the thickness of the bag when containing a volume of 57 mls is 57 cc = 9.3cm x 10.2 cm x Thickness. Solving for T = about 0.6 cm.

Therefore, the substitution of the controlled freezing method of laterally varying thermal gradients for the uncontrolled platelet freezing method described in US 4,131,200 would have been obvious for the advantages taught in US 5,873,254, such as improved viability of cells.

One of ordinary skill in the art would have been motivated at the time of invention to make these substitutions/variations in order to obtain the results as suggested by the references with a reasonable expectation of success. The claimed subject matter fails to patentably distinguish over the state of the art as represented by the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

Response to Arguments

Applicant's arguments filed 2/26/08 have been fully considered but they are not persuasive. Previous rebuttals may be found in the previous office actions and are not repeated.

Applicant argues that in small samples, the outer and inner zones change their temperatures essentially at the same rate and that the cited prior art does not teach subjecting the sample to an intermediate temperature until the temperature of the sample in the cross-section is uniform and equals the intermediate temperature, and thus, the presently claimed method is not a mere scaling up of the prior art method.

Please note that “essentially the same rate” is not the same rate. Essentially the same is a relative term, which only means that the rate is not the

same. If a temperature change is applied from the outside of a sample, the inner temperature will equilibrate with the outer temperature at a rate which is limited by the heat transfer rate of the sample. This is true no matter what the size of the sample. This is due the thermodynamics of heat transfer during conduction and is dependent on the thermal conductivity of the sample, $k=Q/t$ times $L/A \times \Delta T$, where k is the thermal conductivity constant, Q is the quantity of heat, t is the time, L is the thickness, A is the surface area and ΔT is the change in temperature. Please notice that all samples have thickness, therefore have positive rates of heat transfer. Only if the sample has no dimensions is heat transfer infinitely large and therefore, truly instantaneous or "the same".

With regard to the "pausing" of the sample at one temperature or uniformity of temperature in the sample, please see col. 6, l. 64 of the prior art reference where the sample spends about 10 minutes inside block 14 at constant temperature of -7°C, then decreases the temperature again to-35°C at a rate of 0.3°C/min. This appears to be a pausing at an intermediate temperature which according to applicant's arguments concerning heat transfer rates, would reasonably be enough time to equilibrate the sample in any cross-section. Also, in applicants arguments on page 15, applicant states that uniformity may be achieved by methods (a), (b) or (c). It appears that method (c) was exemplified in col. 6, l. 64 of the prior art reference.

Applicant is urged to look carefully at the exemplification in an effort to uncover and present unexpected results commensurate in scope with the claims. Also, a decrease in the number of independent claims would simplify prosecution.

Conclusion

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). It is applicants' burden to indicate how amendments are supported by the ORIGINAL disclosure. Due to the procedure outlined in MPEP 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 USC 102 or 35 USC 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (571) 272-0922. The examiner can normally be reached on Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, M. Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sandra Saucier/
Primary Examiner
Art Unit 1651